claims is found throughout the specification. Reconsideration is respectfully requested.

A. 35 USC § 121 -

Restriction was required between the lyophilized compositions and the method for making the composition. Applicants elect the claims directed to the compositions (i.e., claims 1 to 8 and 10) for prosecution in this application.

It was further determined that if generic claims of the application are not ultimately held allowable, the application would contain claims directed to two patentably distinct species, to wit: claims 1, 2, 6 to 8 and 10 and claims 3 to 5. Applicants are thus required to elect a single species for examination. Accordingly, without prejudice, Applicants provisionally elect claims 1, 2, 6 to 8 and 10 for examination in order to advance the prosecution of this application.

B. 35 USC § 112, first paragraph -

The specification and claims stand objected to and rejected under 35 USC 112, first paragraph, for lacking an enabling disclosure. Applicants respectfully traverse these rejections and objections.

The specification was objected to because page 6, lines 29 to 32, were thought to be confusing. Applicants have amended the specification in order to make the description clearer. Basis for this amendment is found in the earlier passage, in Figure 2, and in claim 8.

The specification was objected to because only salts of citric acid, tartaric acid, aspartic acid and glutamic acid were exemplified. In order to facilitate the prosecution of this application, Applicants have limited the claims to these salts, along with isocitric acid, which finds basis on page 6, line 5. This amendment is made without prejudice to Applicants pursuit of the subject matter in a later, related application.

The specification was also objected to for only enabling sucrose and trehalose. In order to facilitate the prosecution of this application, Applicants have limited the relevant claims to these sugars. This amendment is made without prejudice to Applicants pursuit of the subject matter in a later, related application. In view of these amendments Applicants believe this objection/rejection should be withdrawn.

It was suggested that claim 1 should recite the ratios of gonadotropin to dicarboxylic acid. In order to facilitate the prosecution of this application, Applicants have amended claim 1 as requested. This amendment is made without prejudice to Applicants pursuit of the subject matter in a later, related application.

It was suggested that the amount of non-ionic surfactant should be stated in claim 3. Applicants have amended claim 3 to define, functionally, the amount of surfactant present. Basis for the amendment is found on page 8, lines 6 to 13.

The subject matter of claim 8 was not found in the specification. Applicants have now amended the specification to specifically include the material set forth in original claim 8.

The specification was objected to for not providing support for ionic strength. Applicants respectfully traverse this rejection, and wish to direct the Examiner's attention to page 6, lines 13 to 23, and Figure 1. The calculation of the ionic strength of a solution is well known to those of skill in the art based on the concentrations and the valences of all ions present in the solution. The ionic strength is defined mathematically as $\mu = \frac{1}{2}\Sigma c_i z_i^2$, where c_i is the concentration of ion I in mol/liter, z_i is the valence of ion i and Σ is the summation of the product of the concentration and the square of the valence of each ion in the solution. See, e.g., the enclosed page 228 of Remington's, which was cited in the original specification on page 6, lines 21-24. Using this formula, one calculates the numbers used in the specification and Figure 1 (which depicts ionic strength as "I X

1000"). Figure 1 clearly depicts the relationship between ionic strength and percentage recovery in various systems according to the invention; generally the greater the ionic strength of the solution ultimately freeze dried, the greater the recovery.

The specification was also objected to for assertedly failing to teach how to make a composition containing dicarboxylic acid salts plus non-ionic surfactants. Applicants respectfully traverse this rejection, and wish to direct the Examiner's attention to page 8, lines 15 to 35, which describes a process for making such compositions generally; page 7, line 22 to page 8, line 15, which describes the desirability of the non-ionic surfactant component generally; page 9, line 24 to page 10, line 1, which describes a "highly preferred stabilized lyophilisate" containing a non-ionic surfactant such as "Tween 20"; and Examples I, VII and VIII, all of which describe compositions containing a non-ionic surfactant. For further support and to provide data establishing the utility of the non-ionic surfactant, Applicants herewith submit a Declaration under 37 CFR 1.132, which supports the desirability of adding a surfactant. Looking at the data presented one sees that the recovery is greatly enhanced in comparison to solutions without the surfactant, especially after contact of the solution with, for example, silicone tubing.

C. 35 USC § 112, second paragraph -

The claims were rejected for being indefinite under 35 USC §112, second paragraph. Applicants have amended the claims and traverse the rejection.

"Stabilized" was considered unclear. Applicants respectfully disagree, and wish to point out the fact that such terminology is well known and accepted in the art as exemplified by the four patents cited against the present application, all of which use the same or similar terminology. However, to facilitate the prosecution of this application, Applicants have removed the terminology from the claims, and have substituted the functional

definition of the term found in the specification. (Page 5, lines 3 to 13 of the specification).

The claims were also rejected for use of the terminology "effective amount". Although these words are commonly used claim language when combined with functional terms, as in the present claims, they have been deleted by amendment, without prejudice, in order to advance the prosecution of the application. It was also suggested that the specific amounts or ratios of gonadotropins and dicarboxylic acid salts should be recited, as well as the identity of the salts. As discussed previously, Applicants have, without prejudice, amended the claims to include these parameters.

Claims 7 and 10 were considered indefinite for use of the terms "one type" and "two types" and for not further limiting the claims from which they depend. Applicants have amended these claims to overcome the rejections under 35 USC § 112 and, in view of the amendment, request that the rejections be withdrawn.

D. Claims 1, 2 and 6 - 10 and 35 USC §103-

Claims 1, 2 and 6 - 10 were rejected under 35 USC § 103 for being obvious over Kawaguchi et al. or Hamilton et al. Applicants respectfully traverse this rejection.

Kawaguchi et al. discloses lyophilized erythropoietin preparations assertedly stabilized with various compounds. Among the compounds listed in Kawaguchi et al. are sodium citrate and sucrose, which are identified as stabilizing erythropoietin. As acknowledged by the Examiner, Kawaguchi et al., however, fails to teach gonadotropin(s) or specific amounts of citrate salts.

Another shortcoming of the Kawaguchi et al. reference is that its teachings cannot be reliably or predictably applied to the case at hand. Besides sodium citrate and sucrose, Kawaguchi et al. also identifies maltose (column 1, line 67) and mannitol (column 2, line 1) as compounds that stabilize erythropoietin. When Applicants tried to stabilize gonadotropins with these same compounds, they were found to actually destabilize the

gonadotropins (see, e.g., page 10, lines 1 to 6 of the specification and Example I.A., wherein maltose is compared to sucrose and trehalose in stabilizing recombinant source FSH). Kawaguchi et al. fails to suggest the preference for a non-reducing sugar.

Kawaguchi also does not teach the criticality of a dicarboxylic acid salt for stabilizing gonadotropins. As shown in Example I.B. in the specification, attempts to stabilize a gonadotropin without a dicarboxylic acid salt resulted in almost exclusive oligomer formation, while the gonadotropin stabilized with the dicarboxylic acid showed no such degradation products. Kawaguchi et al. does not teach or suggest such an unexpected result. In fact Kawaguchi et al. report a 96% residual erythropoietin activity using exclusively sucrose as a stabilizer (column 3, line 39 of Kawaguchi et al).

Kawaguchi et al. also fails to identify salts of tartaric acid, aspartic acid, isocitric acid, and glutamic acid (new claim 12), the correlation between ionic strength and recovery (new claims 11 and Figure 1 of present specification), the use of trehalose (new claim 13), and the stabilization of more than one gonadotropin (claims 10).

In view of these differences, Kawaguchi et al. cannot be said to make Applicants' invention obvious.

Hamilton, Jr. et al. discloses the stabilization of growth hormone through the use of non-reducing sugars and various other compounds, including choline derivatives, such as choline bitartrate and tricholine citrate, especially in an aqueous environment. In reviewing the reference, Applicants were not able to find any indications that the compositions of Hamilton, Jr. et al. were freeze dried or lyophilized. In fact, in the described "dry state", the Hamilton, Jr. et al. composition is a "dry mixture comprising solid growth hormone and solid stabilizer." (Column 2, lines 58-65 of Hamilton, Jr. et al.). It therefore does

not disclose Applicants' invention, which involves pre-mixing a stabilizer with a gonadotropin and then freeze drying it to form a stable lyophilisate. It is merely a dry mixture. This is further confirmed by the Examiner's observation that the ratios of dicarboxylic acids salts to non-reducing sugars recited in the claims are not disclosed in the art because Hamilton, Jr. et al. did not freeze dry his compositions and did not discover Applicants' invention.

As also acknowledged by the Examiner, Hamilton, Jr. et al. does not teach the hormone gonadotropin or the amounts of stabilizers in the combination.

Regarding the citrate compositions, the citrate is only present as "derivatives of choline". (Column 4, lines 51-57). Hamilton, Jr. et al. does not teach that a dicarboxylic acid salt is important, let alone critical for the stabilization of gonadotropins. The reference teaches that the choline portion is important.

Furthermore, as previously stated with regard to the Kawaguchi et al. reverence, the teachings of Hamilton, Jr. cannot be readily applied to the present invention. Contrary to what Hamilton, Jr. et al. reports, non-reducing sugars by themselves are insufficient to stabilize gonadotropins. Hamilton, Jr. et al. themselves encountered a similar problem with prior art polyols, as not all were found to stabilize growth hormones. (Column 4, lines 3-6 and column 9, line 67 to column, 10, line 33). The stability of various proteins, or even the same proteins from various sources (see, e.g., the enclosed Declaration wherein gonadotropins from urinary sources are inherently more stable than gonadotropins of recombinant source) with various stabilizers, is just not sufficiently predictable to make the invention obvious. This observation is in line with the general rule in chemical inventions that "in arts such as chemistry it is not obvious from the disclosure of one species [i.e. one hormone or protein], what other species will work". MPEP § 706.03(z). Different proteins

are different, with different molecular weights, isoelectric points, solubilities, glycogen portions, stabilities, and etc., and what is known about one cannot predictably be said to be applied to another.

Regarding the rejection of claim 9, i.e., that "the nominal method of mixing the components and lyophilizing them" is not the critical portion of claim 9, it is freeze drying the admixture at a temperature greater than -35°.

Under these circumstances, Applicants believe that the claims should not be rejected for being obvious over Hamilton, Jr. et al. or Kawaguchi et al.

E. Claims 3 - 5 and 10 and 35 USC § 103-

Claims 3 - 5 and 10 were rejected under 35 USC § 103 for being obvious over Yasushi et al. or Hirao et al. Applicants respectfully traverse this rejection.

Yasushi et al. teaches the stabilization of the protein interleukin-2 via the addition of human serum albumin ("HSA"). Although a dicarboxylic acid and undefined "surfactant" may be present in the HSA containing composition, the reference does not teach that any of these compounds acts to stabilize a protein, let alone that the addition of a dicarboxylic acid salt is critical for the stabilization of a freeze dried gonadotropin composition. The succinic, tartaric or citric acid is added specifically as a "buffer" for the IL-2 (column 2, lines 67-68 and column 3, lines 12-13 of Yasushi et al.), while no purpose at all is ascribed to the optional, undefined surfactant component. Yasushi et al. even teaches away from Applicants' invention by preferably including a reducing compound.

Furthermore, Yasushi et al. does not disclose that more than one gonadotropin may be stabilized by the addition of a dicarboxylic acid salt, or that the ionic strength of a stabilizer has any importance in stabilizing a gonadotropin containing composition.

Hirao et al. discloses the stabilization of the protein fibrinonectin with disaccharides, albumin or non-ionic surfactants. Again, Hirao et al.'s teachings cannot be automatically applied to the instant invention, which is evident from Hirao et al.'s choice of disaccharides. Hirao et al. teaches that maltose can be used to solubilize fibrinonectin, while Applicants found that it actually destabilizes gonadotropins. Hirao et al. also teaches that sucrose alone can act to stabilize fibrinonectin, while Applicants found this not to be the case of gonadotropins, a dicarboxylic acid salt is always required.

Until now, no one has been able to successfully stabilize extremely pure gonadotropin containing compositions, especially gonadotropins of recombinant source or compositions containing more than one gonadotropin. Applicants, unexpectedly, have found that it could be done using a dicarboxylic acid salt at a certain ionic strength.

The addition of a non-reducing sugar or non-ionic surfactant for use with the dicarboxylic acid salt also increases the desirability of Applicants' invention for both process and use reasons. None of this is suggested by the prior art.

Applicants' way of stabilizing the gonadotropin could not be predicted by the prior art. What works for one protein will not necessarily work for another, as clearly demonstrated by the art of record, and as generally accepted in the field. According to generally accepted patent law, absent some reasonable expectation of success, Applicants' invention cannot be said to be obvious.

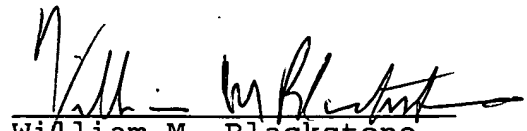
In view of the amendments and remarks, Applicants believe the application is in condition for allowance. Favorable action is solicited. In the event questions remain after this response, the Examiner is invited to telephone Applicants' attorney at the number below.

Submitted herewith is a copy of the cited section of Remington's Pharmaceutical Sciences and a copy of a Declaration by Dr. Skrabanja. The original of the Skrabanja Declaration is being

mailed to the undersigned and will be submitted when it is received.

In the event any fees are required with this paper, please charge our Deposit Account No. 02-2334, for which purpose duplicate copies are enclosed.

Respectfully submitted,



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Enclosures

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